Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 257 (2003) 217–225
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Migration of antioxidant additives from various polyolefinic plastics into oleaginous vehicles

B. Marcato [a], S. Guerra [a], M. Vianello [a], S. Scalia [b,*]

[a] *Basell Polyolefins, G. Natta Research Centre, 44100 Ferrara, Italy*
[b] *Department of Pharmaceutical Sciences, University of Ferrara, Via Fossato di Mortara 17, 44100 Ferrara, Italy*

Received 17 October 2002; received in revised form 31 January 2003; accepted 10 February 2003

Abstract

The migration of the antioxidant additives pentaerythrityl tetrakis(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate (Irganox 1010) and tris(2,4-di-*tert*-butylphenyl)phosphite (Irgafos 168) from polyolefinic packaging into oily vehicles was investigated. The polyolefins included in the study were from the following classes: isotactic polypropylene homopolymer (PP), ethylene-*co*-propylene random copolymer (RACO), ethylene-propylene heterophasic copolymer and ethylene-propylene amorphous copolymer blend (EP) and high-density polyethylene (HDPE). Each polymer was additioned with Irganox 1010 (0.15%, w/w) and Irgafos 168 (0.15%, w/w) and processed into blown bottles. To study the antioxidant release process, plastic sheets were cut from the bottles and dipped for various time intervals into a mixture of five oils (caprylic/capric triglyceride, cyclomethicone, dicaprylyl ether, isohexadecane and $C_{12–15}$ alkyl benzoate) representative of lipophilic excipients used in pharmaceutical and cosmetic formulations. After exposure to the oil medium, the non-migrated Irganox 1010 and Irgafos 168 were recovered from the polymeric matrices using microwave-assisted extraction with ethyl acetate-hexane and assayed by HPLC. The leaching of the two antioxidants varied remarkably depending on the polyolefin crystallinity and structure. The amount of Irganox 1010 transferred into the contact medium at 25 °C decreased in the order EP > RACO > PP > HDPE. The same polyolefin ranking was observed in the case of Irgafos 168, except for PP and HDPE which exhibited similar depletion of this additive. Migration of Irgafos 168 was greater than that of Irganox 1010 and the release of both antioxidants increased at higher temperature (50 °C). The obtained data are useful for the selection of polyolefinic matrices as raw-materials for the production of pharmaceutical and cosmetic containers.

Keywords: Polyolefins; Antioxidant additives; Containers; Migration; Oily vehicles

1. Introduction

Plastics are the most commonly used materials for the packaging of food, pharmaceuticals and cosmetics (Schwope et al., 1987; Stöffler, 1991; Yagoubi et al., 1993). Among the plastic polymers, polyolefins exhibit several advantages including low production cost, good resistance and protection of the content and reduced environmental impact (Stöffler, 1991; Ferrara et al., 2001). In addition, because of their inertness, polyolefins are suitable for applications requiring compliance with health and safety regulations, such as food packaging and medical delivery systems (Ferrara et al., 2001; European Pharmacopoeia, 2001). Commercial polyolefins need the addition of stabilizers, primarily antioxidants, to preserve their

* Corresponding author. Tel.: +39-0532-291277; fax: +39-0532-291296.
E-mail address: sls@unife.it (S. Scalia).

0378-5173/03/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0378-5173(03)00143-1

chemical and physical–mechanical properties both during processing and under the conditions of use (Marcato and Vianello, 2000; Ferrara et al., 2001; Haider and Karlsson, 2002). Since international regulatory authorities (EEC Directive, 1997; European Pharmacopoeia, 2001) require that pharmaceutical and food packaging should not interact physically or chemically with their contents, the possible release of the polymer additives by the plastic containers should be monitored and minimized.

A large number of publications have appeared in the literature concerning the migration of antioxidant additives from food, drug and cosmetic plastic packages to their content (Figge and Freytag, 1980; Pellerin et al., 1984; Yagoubi et al., 1993; Garde et al., 1998). Detailed investigations have been carried out on the release of plastic additives by food containers using hydrophilic and lipophilic contacting media as food simulants (Bieber et al., 1985; Schwope et al., 1987; Garde et al., 1998). Less information is available on the transfer of the antioxidant stabilizers from plastic packaging into pharmaceutical and cosmetic products, the majority of studies being performed on aqueous formulations (Figge and Freytag, 1980; Smistad et al., 1989; Yagoubi et al., 1993). However, because of the lipophilic character of the antioxidants, their migration process from the packaging to hydrophilic preparations might be limited by the dissolution of migrants on the contacting polymer surface. Therefore for an accurate evaluation of pharmaceutical- and cosmetic-packaging interactions, it is important to examine the depletion of container additives in lipidic environments with high antioxidant extracting power.

The present study reports on the migration of antioxidants from different polymeric materials into oily vehicles. In particular the investigation focuses on polyolefinic-based packaging since these polymers are the primary raw-materials for the production of drug and cosmetic plastic containers (Stöffler, 1991; Romanowski and Schueller, 1997; European Pharmacopoeia, 2001). The two antioxidants (Fig. 1), pentaerythrityl tetrakis(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate (Irganox 1010) and tris(2,4-di-*tert*-butylphenyl)phosphite (Irgafos 168) were selected for the release kinetic studies since they are commonly used concurrently to stabilize polyolefins during processing and in the final container

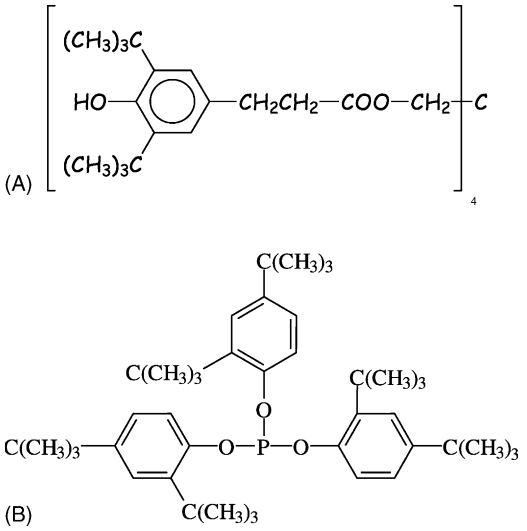

Fig. 1. Chemical structures of Irganox 1010 (A) and Irgafos 168 (B).

(Marcato and Vianello, 2000; Haider and Karlsson, 2002).

2. Materials and methods

2.1. Materials

The polymer materials were produced by Basell NV Hoofddorp (The Netherlands). The polyolefins included in the study were: isotactic polypropylene homopolymer (PP); ethylene-*co*-propylene random copolymer (RACO); ethylene-propylene heterophasic copolymer and ethylene-propylene amorphous copolymer blend (EP); high-density polyethylene (HDPE). All the polymers were stabilized by incorporation of the two antioxidants Irganox 1010 (0.15%, w/w), Irgafos 168 (0.15%, w/w) and of the antiacid agent calcium stearate (0.05%, w/w). Each polyolefin was processed using the blow extrusion technique (Product Development Laboratory, Basell, Ferrara, Italy) into 1-l bottles with the same dimensions and thickness (0.5 mm; Magna-Mike thickness-meter, Panametric, Waltham, MA). Irganox 1010 and Irgafos 168 were supplied by Ciba Speciality Chemicals (Basle, Switzerland). The following oils were used for the migration experiments: caprylic/capric

triglyceride (Arlamol M812; ICI Italia, Milan, Italy), cyclomethicone (Arlamol D4; ICI), dicaprylyl ether (Cetiol OE; Henkel, Fino Mornasco, Italy), isohexadecane (Arlamol HD; ICI) and $C_{12–15}$ alkyl benzoate (Finsolv TN; Polichimica, Bologna, Italy).

Acetonitrile, water and isopropanol were high-performance liquid chromatographic (HPLC) grade from Merck (Darmstadt, Germany). All other chemicals were of analytical reagent grade (Carlo Erba, Milan, Italy).

2.2. X-ray diffractometry

The degree of crystallinity (χ%) of the polyolefinic matrices was determined by X-ray diffractometry (Statton, 1967) using a PW 1710 powder diffractometer (Philips, Eindhoven, The Netherlands) with Cu Kα X-ray beam excited at 40 kV.

2.3. High-performance liquid chromatography

HPLC analysis was carried out on a Model 5500 chromatographic system (Varian, Palo Alto, CA, USA) linked to a Model 7125 injection valve with a 10 μl sample loop (Rheodyne, Cotati, CA, USA) and a Model UV200 variable wavelength UV detector (Varian) set at 273 nm. Data acquisition and processing were accomplished with a workstation using Star software (Varian). Separations were performed on a 4-μm Superspher 60 RP-8 column (125 mm × 4 mm i.d.; Merck) eluted with a linear gradient of water–acetonitrile–isopropanol at a flow-rate of 1.3 ml/min. The elution program is described in Table 1. The identity of the separated peaks was assigned by co-chromatography with authentic standards of Irganox 1010 and Irgafos 168. Quantification was carried out by integration of the peak areas using the external standardization method.

Table 1
Gradient elution program for the HPLC analysis of Irganox 1010 and Irgafos 168 extracted from the polyolefins

Time (min)	Water (%)	Acetonitrile (%)	Isopropanol (%)
0	15	85	0
10	0	65	35
14	0	40	60
16	0	40	60

2.4. Sample preparation

Microwave-assisted extraction was used for the isolation of the two antioxidants, Irganox 1010 and Irgafos 168, remaining in the polyolefinic matrices after the migration tests. The extraction was performed according to the procedure described earlier (Marcato and Vianello, 2000) with minor modifications. In brief, the plastic sheet (ca. 2.5 g) was accurately weighed and cut into small pieces. The obtained sample was loaded into the microwave extraction vessel, mixed with 25 ml of ethyl acetate-hexane (75:25, v/v) and heated for 15 min in the microwave oven (MES-1000 microwave extraction system, CEM, Mathews, NC, USA) with 1000 W microwave power supply. The extraction temperature was set at 110 °C (EP) or 125 °C (PP, HDPE, RACO), according to the polymeric material. After extraction, the vessel was allowed to cool to ambient temperature, the ethyl acetate-hexane phase was filtered (0.45 μm PTFE membrane filters; Alltech Italia, Milan, Italy) and analyzed by HPLC.

2.5. Migration studies

The test samples were obtained by cutting longitudinal sections (15 cm × 3.5 cm; thickness, 0.5 mm) from the bottles prepared with the four different polyolefinic materials. The plastic strips were inserted into glass grid supports to keep the samples separated, in a vertical position and suspended in the migration medium. The resulting stack was introduced into a 3-l glass beaker containing an oil mixture composed of equal volumes of Arlamol M812, Arlamol D4, Cetiol OE, Arlamol HD and Finsolv TN. The kinetics of the antioxidant release were studied at room temperature (25 °C) and at 50 °C. At appropriate time intervals, the plastic sections were retrieved and the excess oil present on the surface was removed by pressing them between two filter paper sheets for 30 s with a 1 kg plate. The resulting sample was then subjected to microwave-assisted extraction and HPLC assay as outlined above. The release profiles were obtained by plotting the remaining concentration (% of initial) of the antioxidant in the polyolefin matrix versus time. All tests were run in triplicate.

3. Results and discussion

The release of the two antioxidants, Irganox 1010 and Irgafos 168, by polyolefinic packaging was studied after exposure of the plastic matrices to a medium composed of equal proportions (v/v) of five oils commonly used in the formulation of pharmaceuticals and cosmetics (Cosmetic Ingredient Dictionary, 1982; Martindale, 1999). The mixture included lipids of various chemical structures (hydrocarbons, silicones, triglycerides, ethers, alkyl benzoates) and is representative of commercial preparations which are generally based on combination of several oils with different properties (Salka, 1997; European Pharmacopoeia, 2001). For the release test a lipophilic medium was selected because it acts as an effective solvent for the hydrophobic Irganox 1010 (log P, 18.8) and Irgafos 168 (log P, 17.6). Under these conditions, dissolution of the two stabilizers diffused to the polymer surface is favored and does not represent a limiting step in the process of additive migration, as in the case of hydrophilic contact media (Garde et al., 1998). In fact, transfer of antioxidants from plastic packaging has been found to be greater into fat than into emulsion or aqueous food simulants (Bieber et al., 1985; Garde et al., 1998).

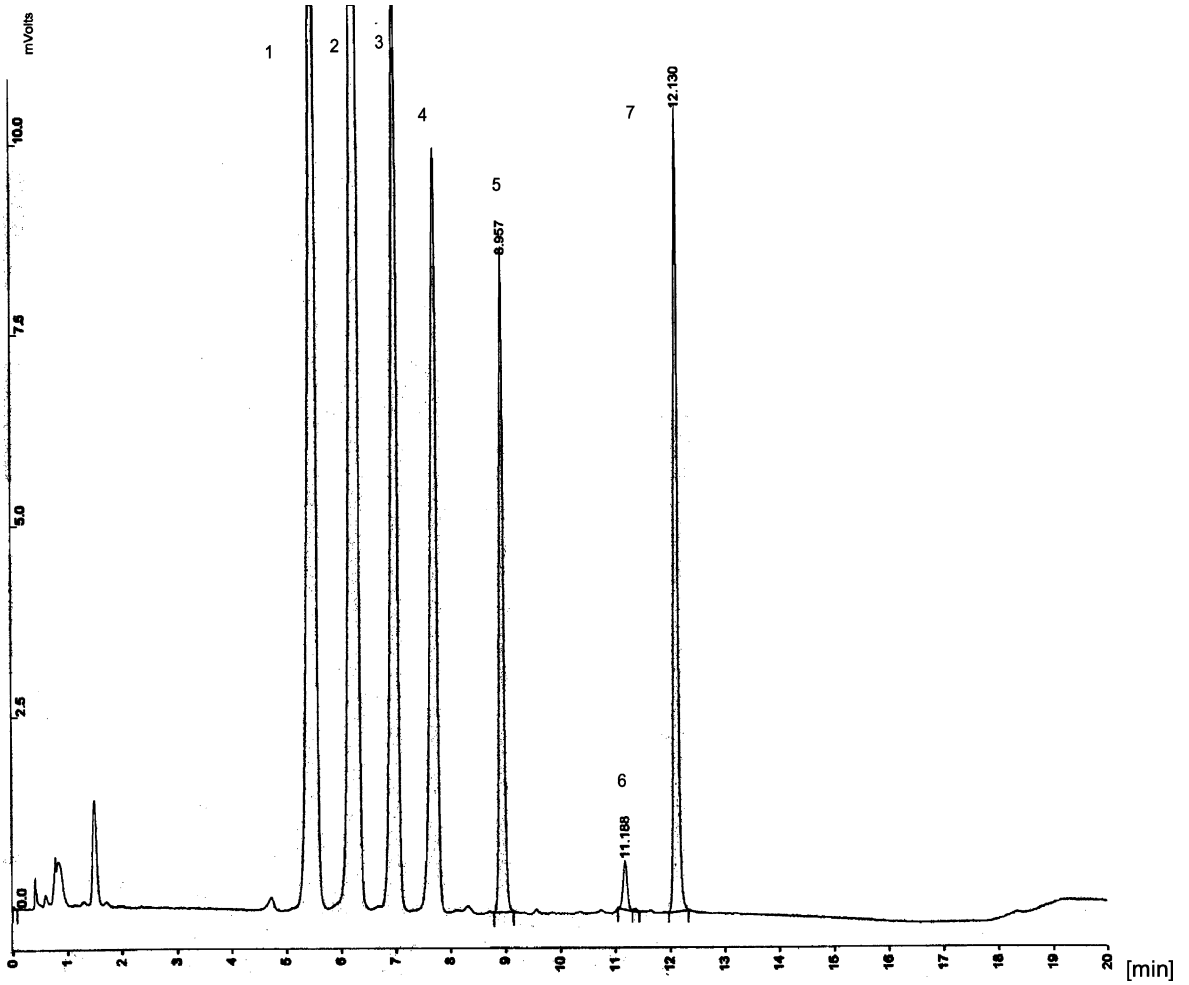

Fig. 2. HPLC chromatogram of a sample containing the oil mixture and the antioxidants. Peaks: 1–4, alkyl benzoates; 5, Irganox 1010; 6, Irgafos 168 phosphate (oxidizing product of Irgafos 168); and 7, Irgafos 168. Operating conditions as described in Section 2.

In a previous paper (Marcato and Vianello, 2000) we reported a rapid procedure for the assay of several additives, including Irganox 1010 and Irgafos 168, in polyolefins using microwave-assisted extraction and HPLC analysis. This method proved not to be applicable to the determination of the non-migrated antioxidants in the plastic material exposed to the oil mixture, owing to overlapping of a peak from the $C_{12–15}$ alkyl benzoates with Irganox 1010. By varying the gradient elution conditions (see Table 1) and switching from a 5-μm C-18 column to a 4-μm C-8 stationary phase a complete separation of all component peaks was obtained (Fig. 2). In the case of the antioxidant Irgafos 168, both the original phosphite and its reaction product, the corresponding phosphate, were quantitatively determined (Haider and Karlsson, 2002).

In order to take into account the influence of the plastic processing on additive migration (Figge and Freytag, 1984), bottles which are commonly used as package for cosmetics and pharmaceutical dosage forms (Liebe, 1996; Romanowski and Schueller, 1997) were specifically produced with each of the examined polyolefins. These included a polypropylene homopolymer (PP), high-density polyethylene (HDPE) and two ethylene-propylene copolymers (RACO and EP) with different crystalline/amorphous ratios. The distribution of Irganox 1010 and Irgafos 168 in different parts (neck, top, side and bottom) of the obtained containers was also evaluated. The percentage variation of the additive concentrations was <6.5% which indicated a satisfactory antioxidant content uniformity in the packaging. The direct use of the whole container for studying the leaching of additives was not practical due to the large amounts of oils required and the high number of bottles necessary for carrying replicate determinations. To overcome these problems, the kinetic of migration of Irganox 1010 and Irgafos 168 was investigated by placing longitudinal sections of the bottles prepared with the four polymers into a constant-temperature bath of the oil mixture. Preliminary experiments were performed to verify if the criterion of sink conditions was fulfilled during the release tests. Assuming a complete removal of the two additives from the polyolefinic matrices, the concentration of Irganox 1010 and Irgafos 168 in the contact medium will reach less than 1.5% of their solubilities and hence the antioxidant

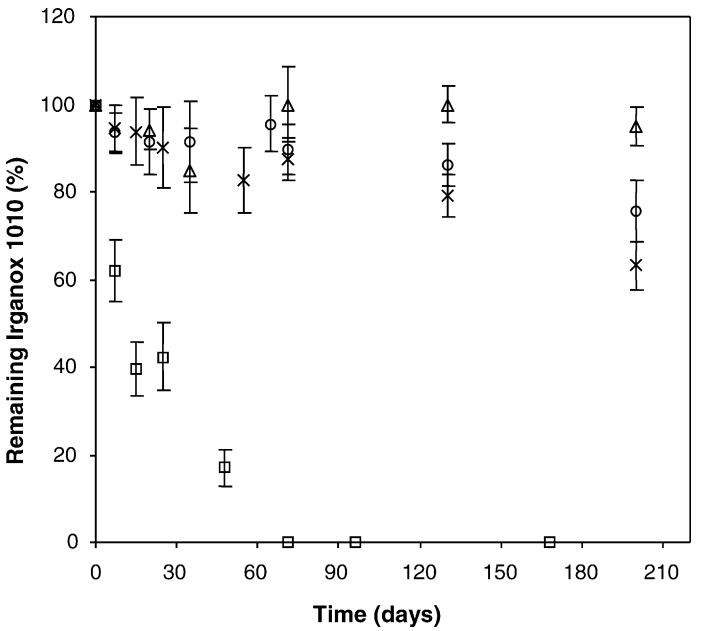

Fig. 3. Concentration profiles (% of initial content) at 25 °C of Irganox 1010 in the various polyolefinic matrices exposed for different times to the oil mixture. Key: (□) EP, (×) RACO, (○) PP, and (△) HDPE. Each point represents the mean ± S.D. of triplicate experiments.

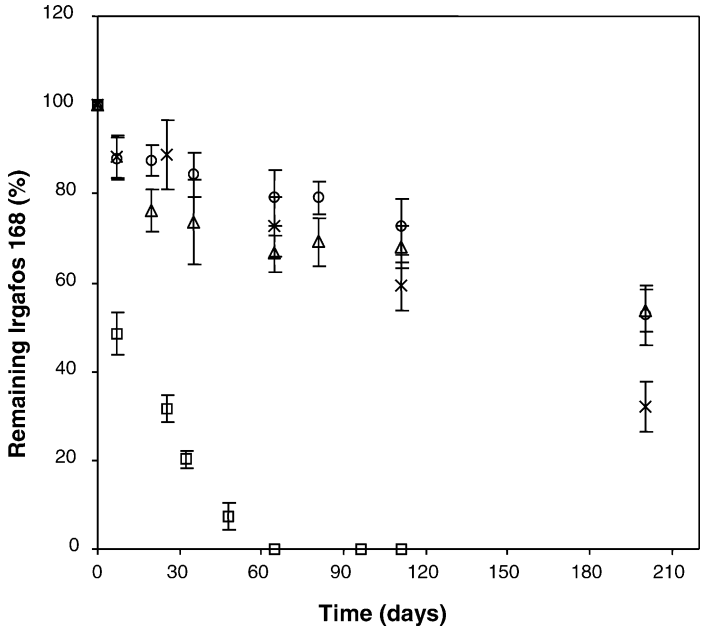

Fig. 4. Percent reduction at 25 °C of Irgafos 168 concentration in the various polyolefinic matrices exposed for different times to the oil mixture. Conditions and symbols as in Fig. 3.

migration rates are not affected by the concentration gradient in the oil phase.

Fig. 3 shows the changes in the level of Irganox 1010 in the different polyolefinic matrices at 25 °C. The amount of antioxidant lost varies remarkably depending on the polymeric material and decreases in the order EP > RACO > PP > HDPE. Migration of the stabilizer was greatest from the EP copolymer with the lowest crystallinity ($\chi = 30\%$), whereas the HDPE matrix with a 70% crystalline fraction showed the minimal depletion of Irganox 1010. The two polyolefins RACO ($\chi = 54\%$) and PP ($\chi = 52\%$) exhibited no significant differences (analysis of variance) in the extent of additive migration which was greater than that observed for HDPE (Fig. 3).

The concentration profiles at 25 °C of Irgafos 168 in the different polyolefins exposed to the oil mixture are illustrated in Fig. 4. The rate of release of the antioxidant was fastest from the EP copolymer, in accordance with the migration behaviour of Irganox 1010 (Fig. 3). On the other hand, the slowest additive transfer into the oil medium was observed for HDPE and PP (Fig. 4). These two polyolefins exhibited similar release patterns despite the marked difference in their χ values ($\chi = 70\%$ for HDPE and $\chi = 52\%$ for PP). Moreover, although RACO and PP have similar crystallinity, the loss of Irgafos 168 was higher from the former polymer. These data indicate that crystallinity is not the only factor influencing the antioxidant leaching but also the polymer structure plays an important role. The results shown in Figs. 3 and 4 demonstrate that the migration of the lower molecular weight Irgafos 168 proceeds faster than that of Irganox 1010.

The data generated at 50 °C for the leaching of Irganox 1010 and Irgafos 168 from the different classes of polyolefins are reported in Figs. 5 and 6, respectively. As expected, for both antioxidants the release kinetics increased at higher temperature. In several experiments the polymers became completely depleted of the stabilizers prior to the end of the exposure period. Under these conditions too, Irgafos 168 migrates more rapidly than Irganox 1010. As regard to the different polyolefins, the data obtained at 50 °C indicate that the fastest loss of Irganox 1010 was found from the EP matrix (Fig. 5). The rate of transfer of the additive into the contact medium was reduced in the case of RACO and PP plastics and was lowest from HDPE. Under the testing conditions,

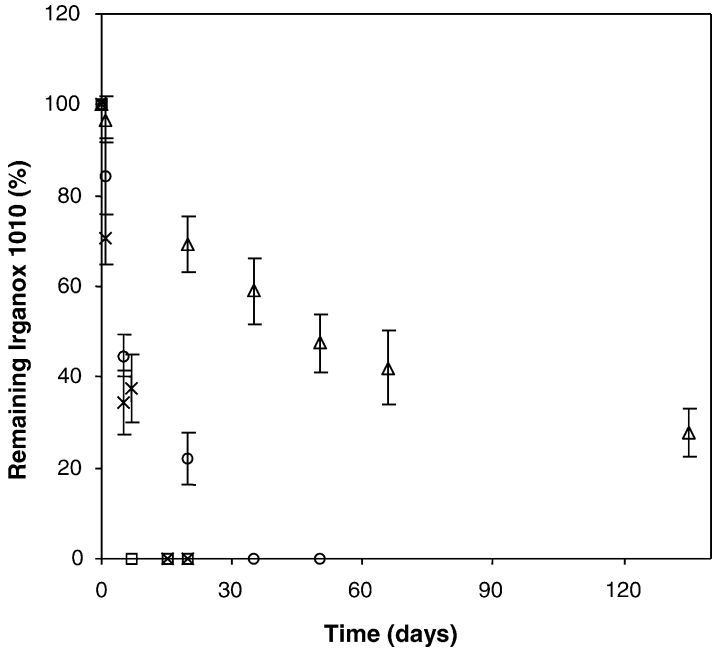

Fig. 5. Levels of Irganox 1010 (% of initial content) in the various polyolefinic matrices exposed for different times to the oil mixture at 50 °C. Conditions and symbols as in Fig. 3.

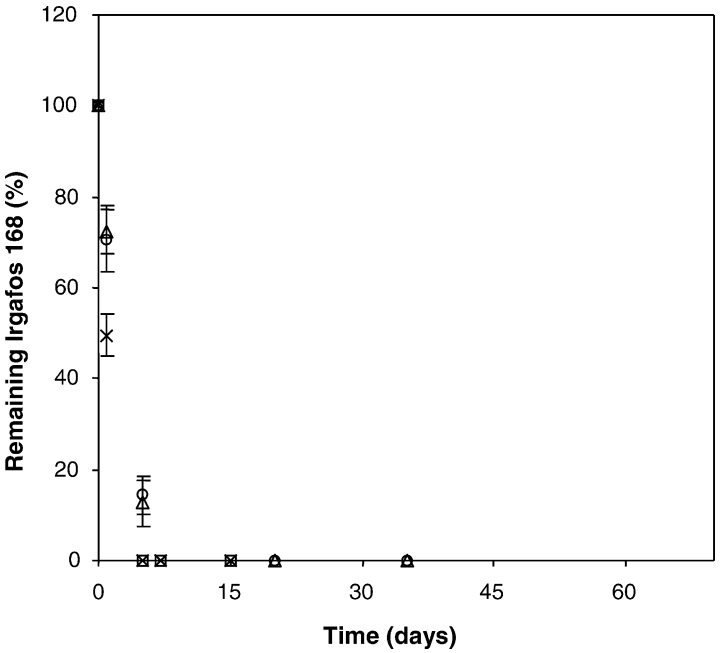

Fig. 6. Percent variation at 50 °C of Irgafos 168 concentration in the various polyolefinic matrices exposed for different times to the oil mixture. Conditions and symbols as in Fig. 3.

Table 2
Percentages of antioxidants left in the polyolefin bottles filled with the mixture of five oils (Arlamol M812, Arlamol D4, Cetiol OE, Arlamol HD and Finsolv TN) and stored at 25 °C for 1 year

Polyolefin bottles	Antioxidant left (%)[a]	
	Irganox 1010	Irgafos 168
HDPE	92.7 ± 5.7	47.8 ± 5.2
PP	76.3 ± 7.1	47.0 ± 4.1
RACO	57.9 ± 6.3	36.4 ± 4.7
EP	0	0

[a] Each value represents the mean ± S.D. of three determinations.

the Irgafos 168 release kinetics at 50 °C were too fast for an accurate comparison of the different polymeric matrices. However, the concentration of Irgafos 168 was found to decrease slightly slower in PP and HDPE as compared to RACO and EP (Fig. 6).

In order to validate the methodology used for the migration tests, some of the bottles produced with the examined polymers were filled with the foregoing oil mixture and maintained at 25 °C for 1 year. The percentages of Irganox 1010 and Irgafos 168 remaining in the different polyolefin-based containers are listed in Table 2. The obtained results exhibit the same trend observed for the plastic sheets (see Figs. 3 and 4). This indicates that the latter system is suitable for simulating the actual conditions in the finished product.

4. Conclusions

The results described in this study demonstrate that the migration of the major antioxidants Irganox 1010 and Irgafos 168 from polyolefinic packaging into oleaginous vehicles varies according to the polymer crystallinity grade and structure. The extent of additive release was greater from polyolefins with high content of amorphous fraction (e.g. EP) and hence these materials are not suitable for the production of packaging in direct contact with the oils. In fact, a marked migration of the antioxidants not only alters the content quality but can also affect the polymer stability under the application conditions. On the other hand, the loss of Irganox 1010 and Irgafos 168 from polyolefinic materials is reduced when PP and especially HDPE are selected for the manufacturer of oil containers. The information obtained on the leaching of the examined additives from the different polyolefinic matrices should also be applicable, in principle, to cosmetic and pharmaceutical formulations (e.g. hydrophilic forms, emulsions) with an antioxidant extraction power lower than oils.

References

Bieber, W.D., Figge, K., Koch, J., 1985. Interaction between plastics packaging materials and foodstuffs with different fat content and fat release properties. Food Addit. Contam. 2, 113–124.

Cosmetic Ingredient Dictionary, 1982. The Cosmetic, Toiletry and Fragrance Association, Washington, DC.

EEC Directive, 1997. Off. J. Eur. Commun. 40, 10–15.

European Pharmacopoeia, 3rd ed., 2001. European Directorate for the Quality of Medicines, Strasbourg, pp. 170, 1665.

Ferrara, G., Bertoldo, M., Scoponi, M., Ciardelli, F., 2001. Diffusion coefficient and activation energy of Irganox 1010 in poly(propylene-*co*-ethylene) copolymers. Polym. Degrad. Stabil. 73, 411–416.

Figge, K., Freytag, W., 1980. Migration of low molecular weight constituents from plastics in cosmetics. Acta Pharm. Technol. 26, 97–115.

Figge, K., Freytag, W., 1984. Additive migration from various plastics with different processing or properties into test fat HB 307. Food Addit. Contam. 1, 337–347.

Garde, J.A., Catala, R., Gavara, R., 1998. Global and specific migration of antioxidants from polypropylene films into food simulants. J. Food Protect. 61, 1000–1006.

Haider, N., Karlsson, S., 2002. Loss and transformation products of the aromatic antioxidants in MDPE film under long-term exposure to biotic and abiotic conditions. J. Appl. Polym. Sci. 85, 974–988.

Liebe, D.C., 1996. Packaging of pharmaceutical dosage forms. In: Banker, G.S., Rhodes, C.T. (Eds.), Modern Pharmaceutics, 3rd ed. Marcel Dekker, New York, pp. 692, 709, 713.

Marcato, B., Vianello, M., 2000. Microwave-assisted extraction by fast sample preparation for the systemic analysis of additives in polyolefins by high-performance liquid chromatography. J. Chromatogr. 869, 285–300.

Martindale, 32nd ed., 1999. The Pharmaceutical Press, London, pp. 1382–1385.

Pellerin, F., Baylocq, D., Andre, D., Majcherczyk, C., Laham, N., 1984. Migrations between plastic containers and liquid pharmaceuticals: general criteria for study and detection methods. Ann. Pharm. Fr. 42, 15–25.

Romanowski, P., Schueller, R., 1997. Cosmetic product packaging. Cosmet. Toil. 112, 65–73.

Salka, B.A., 1997. Choosing emollients. Cosmet. Toil. 112, 101–106.

Schwope, A., Till, D.E., Ehntholt, D., Sidman, K., Whelan, R., Schwartz, P., Reid, R., 1987. Migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. Food Chem. Toxicol. 25, 317–326.

Smistad, G., Waaler, T., Roksvaag, P.O., 1989. Migration of plastic additives from soft poly(vinyl chloride) bags into normal saline and glucose infusions. Acta Pharm. Nordica 1, 279–290.

Statton, W.O., 1967. The meaning of crystallinity when judged by X-rays. J. Polym. Sci. C 18, 33–50.

Stöffler, A., 1991. Packaging cosmetic preparations. In: Umbach, W. (Ed.), Cosmetics and Toiletries. Ellis Horwood, New York, pp. 304–305.

Yagoubi, N., Baillet, A., Mur, C., Baylocq-Ferrier, D., 1993. Determination of phenolic antioxidants in pharmaceutical formulations by liquid chromatography and migration study on HDPE packagings. Chromatographia 35, 455–458.